## REMARKS

Responsive to the Office Action mailed December 28, 2004, and with an extension of time of THREE MONTHS, the present paper is timely filed on or before June 28, 2005. Claims 1, 2 and 95-98 are pending in the Application and under examination.

*Claim Rejections Under 35 U.S.C. § 103*

Claims 1, 2 and 95-98 stand rejected under 35 U.S.C. § 103 as allegedly obvious in view of Jerussi et al., WO 00/32555 ("WO '555"). For reasons stated previously in the Reply and Amendment of August 25, 2004, reasserted by Applicants as if repeated *ipsis verbis* herein, and for the additional reasons given below, Applicants respectfully traverse.

In attempting to establish grounds for the otherwise bald assertion that claims 1, 2, and 95 – 98 are obvious, the Office, citing Ex parte Gray (BPAI 1989), alleges that "the mere purity of a compound, in itself, does not render a substance unobvious." Office Action, p. 2. The Office's reliance on Gray is misplaced and, moreover, intrinsically requires an assumption that is both erroneous and unsupported by the record.

According to Applicants' best understanding, the Office uses the term "purity" in the sense of "assay", the percentage of a sample that consists of the principal compound (here venlafaxine base), and reply according to this best understanding. At page 4, ¶ 3, the Office alleges; "These claims [1-2 and 95 – 98] are simply directed to a purer form of a well-known pharmaceutical compound. Purifying this well-known pharmaceutical is obvious for reasons already stated." This argument is inadequate to support the conclusion that Applicants' claims are obvious for at least two reasons.

First, the difference between Applicants' invntive white crystalline venlafaxine base and the venlafaxine base of the prior art (and hence the patentability of Applicants' claims) does not turn on the purity of the white crystalline solid venlafaxine base that Applicants respectfully submit (and the Office apparently accepts) they were the first to possess. Second, and more important, the argument assumes, *sub silencio*, that color – or lack thereof[1] – is a surrogate for purity (in the sense of assay). Applicants respectfully submit that this

[1] Applicants respectfully submit that it is elementary physics that "white" is the presence of all colors of the visible spectrum and, conversely, "black" is the absence of all color. Applicants and, apparently, the Office use "color" in the sense of a visually identifiable or distinguishable named "color", e.g. yellowness.

implicit assumption that there is an inherent nexus between color and purity (assay) is erroneous, not supported on the record, and apparently relies on "official notice" of scientific information, not common knowledge in the art, within the ken of a member of the Examining Corps without being supported by an Examiner's Affidavit. *See* M.P.E.P § 2144.03.

Applicants respectfully submit that it is well-known that two samples of the same chemical species can be of the same purity (assay), yet have markedly different color. Increasing the assay of a sample, for example by recrystallization, may improve the overall purity (assay) of the sample by reducing or eliminating several impurities that do not absorb visible light, but leave behind traces of species that do[2]. The assay of the sample is improved with no effect on the perceived "color" of the sample. Applicants further respectfully submit that it is well-known that the crystallinity – or crystalline form – of a material, and not the purity (assay) of the material can be dispositive of color. The principle that factors other than simple purity alone control color finds support in both inorganic chemistry and pharmaceutical chemistry.

Graphite and diamond represent an example of this phenomenon known to skilled artisan and routiner alike. A sample of graphite and a sample of diamond of approximately the same carbon assay (that is of essentially the same purity) have markedly different color. Ruby and sapphire are a further example. The markedly different colors of these gem stones are due to very specific trace impurities. The difference between the color of a ruby and the color of a sapphire does not depend on the "assay" (here gross elemental analysis) of the material, but on the presence of particular trace impurities. A brief description of the color of gem stones is given at Tab A.

Absence of an inherent nexus between purity and color as erroneously and improperly assumed by the Office is further and strikingly demonstrated by the compound N-(2'-nitrophenyl)-2-amino-3-cyano-5-methyl thiophene, colloquially designated "ROY". *See* Tab B. This compound can exist in at least three crystalline forms. Each of these forms has a unique color (red, orange, or yellow) determined solely by the crystallinity (crystalline form) of the compound.

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[2] For example, an impurity that absorbed light in the blue region of the visible spectrum would cause the sample to appear "yellowish". See, e.g., Fred W. Billmeyer, Jr. and Max Saltzman, Principles of Color Technology, Chpt. 2. (1966).

That a particular albeit unrecognized or unknown trace impurity, rather than all impurities as reflected in an assay, can be responsible for the color of a pharmaceutical compound is still further demonstrated by the known but as yet not fully understood propensity of paroxetine hydrochloride to exhibit a pink color. For example, according to Avrutov et al. WO02102382, which describes a process for preparing paroxetine hydrochloride substantially free of pink-colored compounds, "it is believed that impurities in paroxetine hydrochloride play a role in the color change to pink." WO02102382, p. 2, ¶ 1. This reference discusses the effect of a **specific** impurity on color. *Id* (emphasis added):

> [One] approach is to measure the degree of **an** impurity identified by a high pressure liquid chromatography ("HPLC") relative retention time ("RRT") of about 1.5. The different UV-spectrum characteristic of **this impurity** has linked the impurity to the development of a pink color. A color change however can occur **even if this impurity is present at low levels**, suggesting that other impurities may also play a role in the change in color. Purification steps to remove this impurity such as by crystallization, extraction, chromatography or other sepraration procedures are often ineffective.

The assumption that color is an inherent surrogate for purity cannot be said to be common knowledge in the art and is pure speculation by the Office. Applicants expressly respectfully request that the Office provide an affidavit as required by M.P.E.P. § 2144.03 or citation to the art in support of the position that color is an inherent indicator of purity (assay)[3].

The Office's reliance on Gray is not only based on an erroneous unsupported assumption, it is arguably misplaced in view of Cofer, In re Cofer, 354 F.2d 664, 666 (C.C.P.A. 1966). Applicants' invention is better analogized on the facts to that of In re Cofer. As Applicants best understand it, the issue in Coffer was whether the therein-claimed product "2,2-B" which was free-flowing and in crystalline form, was obvious in view of prior art disclosing the same chemical compound in the form of a viscous liquid. Applicant-Appellants pointed to the various advantages of their solid crystalline 2,2-B compared to the

[3] Office notice unsupported by evidence should only be taken where the facts asserted to be well-known, or to be common knowledge in the art are "capable of instant and unquestionable demonstration as to defy dispute." *In re Ahlert*, 424 F.2d 1088, 1091; 165 USPQ 418, 420 (C.C.P.A. 1970); *In re Zurko*, 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001).

2,2-B of the prior art; for example, better color and high epoxy content *Id.* Holding that the record failed to support a holding that those skilled in the art should have known that 2,2-B would exist in crystalline form, or that it would be known how to obtain such crystals, the court stated:

> There is no explanation in the views of the board or examiner why it should be found from the references or from common knowledge that a person skilled in the art would regard free-flowing crystals of 2,2-B to be obvious. In such circumstances, we are not free to search for speculative reasons that might support the rejection, when it is apparent from those opinions that [the references] were ultimately used only to show that 2,2-B was known as a viscous liquid, and not to suggest that the crystalline form would also exist.

*Id.* The Board had failed to address factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggested the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. *Id.* at 668. In reaching its decision, the court rejected the Board's proposition, apparently adopted by the Office in support of the rejection of the instant claims, that "merely changing the form, purity or another characteristic of an old product...does not render the claimed product patentable." *Id.* at 667.

WO '555 discloses (±)-venlafaxine as a "yellow gum that turned slowly in to pale yellow solid." WO '555, p. 23, line 24. The other art of record is either silent on the important physical characteristics of the venlafaxine base therein disclosed, or discloses venlafaxine base that is an oil. See '078 patent. There is nothing in the record or in any properly-cited knowledge in the art at the time the present invention was made that would have suggested to the skilled artisan of the day that venlafaxine base could or would exist as a white crystalline solid, let alone suggesting how such venlafaxine might have been obtained.

As discussed above, WO '555 discloses (±)-venlafaxine as a "yellow gum that turned slowly in to pale yellow solid." WO '555, p. 23, line 24. The gum, upon sitting, turns into a colored solid. Transformation from gum to solid upon sitting for an undisclosed time strongly suggests that the product of WO '555 is unstable.

Applicants respectfully submit that, at the time the invention defined by the rejected claims was made, the skilled artisan recognized that "gums" were inherently unpredictable. One could not have known if or when a transformation of the product disclosed in WO '555

to a white crystalline solid would occur, or whether the solid would turn back into a gum again. Applicants respectfully submit that, at the time the invention described by the rejected claims was made, the art of record would have deterred the skilled artisan from even attempting to obtain venlafaxine base as a crystalline solid.

Even assuming, *arguendo*, that the art of record does not expressly teach-away from the present invention, a point Applicants do *not* concede, Applicants respectfully submit that the art of record clearly eviscerates any reasonable expectation that the skilled artisan of the day might have harbored that venlafaxine base could exist as a white crystalline solid. This failure to describe a reasonable expectation of success is yet another reason why the present rejection is improper. Simply because Applicants, through their diligent efforts in the face of discouraging prior art, persevered and discovered a white crystalline venlafaxine and a way to make it, is not grounds to say it was obvious that it could be done. The reliance upon hindsight to establish a case of obviousness is improper. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143; 229 USPQ 182, 187 n.5 (Fed. Cir. 1986), ("the references must be viewed without the benefit of hindsight vision afforded by the claimed invention"). The Office is obligated to provide specific references that teach or suggest the white crystalline form instead of using applicant's disclosure to meet its burden of proof.

As Applicants best understand the rejection, the Office relies on "official notice" of presumed common knowledge in the art that color (or lack thereof) is an inherent surrogate for purity. Applicants respectfully submit that, as discussed above, there is nothing in the record to support the Office in taking this official notice and respectfully request an Examiner's Affidavit or prior art citation in support of the official notice.

Applicants respectfully submit that even *if* Gray *were* controlling, the references discussed above demonstrate that color is *not* in inherent surrogate for purity and that color ("whiteness") is not indisputably an inherent feature of a "merely more pure [higher assay] product". Furthermore, Applicants respectfully submit that the Office is using Applicants' discovery of white crystalline venlafaxine base to argue that, because Applicants did it, it was obvious to the skilled artisan of the day to do it and how it could be done. For the forgoing reasons, Applicants respectfully submit that the rejection should be withdrawn.

## CONCLUSION

Applicants respectfully submit that, on the basis of the foregoing remarks, the claims are in condition for allowance, which allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would advance the prosecution of the Application, the Examiner is invited to telephone the undersigned attorney.

## REQUEST FOR EXTENSION OF TIME

Applicants respectfully request a three-month extension of time in which to respond to the Office Action mailed December 28, 2004. The three-month extended period expires on June 28, 2005. Payment of the fee required by 37 C.F.R. § 1.17 is made herewith.

## AUTHORIZATION TO DEBIT DEPOSIT ACCOUNT

The Commissioner is hereby authorized to debit Deposit Account **11-0600** in the amount of **$1,520.00** for the fee due with this paper under 37 C.F.R. § 1.17. Applicants respectfully submit that no further fees are due with this paper. If additional fees are due, the Commission is hereby authorized to debit Deposit Account 11-0600 for any such additional fees. A duplicate of the page is provided herewith.

Respectfully submitted,

KENYON & KENYON

Date: June 27, 2005

By: _____

John B. Starr, Jr.
Registration No. 44,474
One Broadway
New York, NY 10004
Tel.: (212) 425-7200